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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/746,635	Applicant(s) MURTHY ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20 and 24-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,25 and 27-32* is/are rejected.

7)☒ Claim(s) *24,26 and 33-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 10/14/04 is acknowledged and has been entered. Claims 24 and 25 have been amended. Claims 27-38 have been added. Claims 20 and 24-38 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112 / 103

2. In light of Applicant's amendment and arguments, the rejection of claims 24 and 25 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. In light of Applicant's amendment and arguments, the rejection of claim 24 under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)), is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995).

Olsson et al. found that 1) adenylate kinase was concomitantly released with hemoglobin during cell aging, 2) cell aging results in progressive lysis of erythrocytes, 3) adenylate kinase was suitable for monitoring hemolysis due to its extreme storage stability, 4) there was a high degree of correlation between the amount of accumulated hemoglobin and adenylate kinase, 5) and while hemolysis was conventionally measured by measuring extracellular hemoglobin, adenylate kinase activity measurement was also a sensitive and convenient way to follow hemolysis (see page 437, Table 1, and page 445). Olsson et al. determined adenylate kinase activity in plasma by measuring formation of ATP from ADP by firefly luciferase reaction.

Olsson et al. differ from the instant invention in failing to detect hemolysis by determining adenylate kinase activity in serum rather than plasma.

Cruse et al. teach serum sample as an alternative to plasma sample. According to Cruse et al. , serum is more convenient than plasma to use for immunoreactions, i.e. immunoassays, because there is no interference from clotting. See page 274, column 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the plasma sample in the method of Olsson et al. with serum sample as taught by Cruse, to determine erythrocyte kinase activity because serum and plasma are conventional alternative samples used in clinical analysis. One of ordinary skill in the art at the time of the instant invention would have been motivated to substitute serum sample as taught by Cruse for the plasma sample in the method of Olsson because Cruse specifically taught that serum is more convenient than plasma for use in immunoassays because there is no interference that may result from clotting in certain assays.

5. Claims 25 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995), as applied to claim 20 above, and in further view of Matsuura et al. (Journal of Biological Chemistry, 264 (17): 10148-10155 (1989)).

Olsson et al. and Cruse et al. are discussed supra. Olsson et al. and Cruse et al. differ from the instant invention in failing to teach determining erythrocyte adenylate kinase activity using an antibody specific for adenylate kinase.

Matsuura et al. teach that there is an association between adenylate kinase activity (deficiency) in erythrocytes and hemolysis (hemolytic anemia) (see Abstract). Matsuura et al. teach that adenylate kinase (AK1) is present in skeletal muscle, brain, and erythrocyte; thus, adenylate kinase activity has been totally and differentially measured (see page 10148, column 2). Specifically, Matsuura et al. describe immunoblot analysis of human adenylate kinase using antibody (anti AK1 antibody) specific for adenylate kinase (see 10151).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to measure adenylate kinase activity in the method of Olsson as modified by Cruse, using antibody specific for adenylate kinase such as taught by Matsuura because use of antibody in determining the concentration of proteins, antigens, or in this case enzyme, is well known, conventional, and well within ordinary skill.

6. Claims 27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995), and further in view of Matsuura et al. (Journal of Biological Chemistry, 264 (17): 10148-10155 (1989)) as applied to claims 25 and 30 above, and in further view of Koyama et al. (Molecular immunology, (1983 Aug) 20 (8) 851-6).

Olsson et al., Cruse et al., and Matsuura et al. have been discussed supra. Olsson et al., Cruse et al., and Matsuura et al. differ from the instant invention in failing

to teach labeling the adenylate kinase antibody with radioisotope and detecting it by radioimmunoassay.

Koyama et al. teach labeling adenylate kinase antibody with radioisotope and detecting the antibody by radioimmunoassay (See Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to label adenylate kinase antibody as taught in the method of Olsson as modified by Cruse and Matsuura, with radioisotope label and detect it by radioimmunoassay as taught by Koyama, because radioisotope labels and radioimmunoassay constitute obvious modifications of labels and assays for detecting various proteins and antibodies which are routinely varied in the art.

7. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995), and further in view of Matsuura et al. (Journal of Biological Chemistry, 264 (17): 10148-10155 (1989)) as applied to claims 25 and 30 above, and in further view of Criss et al. (Enzyme, (1974) 18 (5): 271-278).

Olsson et al., Cruse et al. and Matsuura et al. have been discussed supra. Olsson et al., Cruse et al., and Matsuura et al. differ from the instant invention in failing to teach detecting the adenylate kinase antibody using immunoprecipitation.

Criss teaches detecting adenylate kinase antibody using immunoprecipitation and analyzing precipitated adenylate kinase isoenzyme bands by Ouchterlony double diffusion analysis. See Abstract.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect adenylate kinase antibody as taught in the method of Olsson as modified by Cruse and Matsuura, using immunoprecipitation as taught by Criss, because immunoprecipitation constitutes an obvious variation of detection methods for detecting various proteins, antigens, and antibodies which are routinely varied in the art.

8. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995), and further in view of Matsuura et al. (Journal of Biological Chemistry, 264 (17): 10148-10155 (1989)) as applied to claims 25 and 30 above, and in further view of Yeh et al. (European journal of biochemistry / FEBS, (1983 Nov 15) 136 (3) 523-9).

Olsson et al., Cruse et al., and Matsuura et al. have been discussed supra. Olsson et al., Cruse et al., and Matsuura et al. differ from the instant invention in failing to teach detecting the adenylate kinase antibody using ELISA technique.

Yeh et al. teach detecting adenylate kinase activity using ELISA. See Abstract.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect adenylate kinase activity as taught in the method of Olsson as modified by Cruse and Matsuura, using ELISA technique as taught by Yeh, because ELISA constitutes an obvious variation of assay methods for detecting various proteins and enzymes, which are routinely varied in the art.

9. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) in view of Cruse et al. (Illustrated Dictionary of Immunology, 1995), and further in view of Matsuura et al. (Journal of Biological Chemistry, 264 (17): 10148-10155 (1989)) as applied to claims 25 and 30 above, and in further view of Stewart (US Patent 5,695,928).

Olsson et al., Cruse et al., and Matsuura et al. have been discussed supra. Olsson et al., Cruse et al., and Matsuura et al. differ from the instant invention in failing to teach labeling antibody with radioactive iodine.

Stewart discloses that radioactive iodine is useful in labeling and detecting various distinct primary antibodies in assays such as radioimmunoassay and ELISA. See column 11, lines 44-57.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to label the adenylate kinase antibody as taught in the method of Olsson as modified by Cruse and Matsuura, using radioactive iodine as taught by Stewart, because radioactive iodine constitutes an obvious modification of labels for use in detecting various proteins, antigens, and antibodies, which are routinely varied in the art.

Response to Arguments

10. Applicant's arguments filed 10/14/04 have been fully considered but they are not persuasive.

A) Applicant argues that Olsson measured total adenylate kinase in the plasma of stored units of red blood cells and determined that the activity correlated with hemoglobin release whereas in the present invention, hemolysis of red blood cells takes place in vivo, and that the natural clearance of erythrocyte adenylate kinase from the blood that occurs in vivo does not necessarily take place in a storage bag.

In response, the basis for diagnosis of erythrocyte hemolysis in Applicant's claimed invention is from the direct correlation seen between release of adenylate kinase, which is released concomitantly with hemoglobin, and red blood cell or erythrocyte hemolysis. This correlation is taught by Olsson, albeit, measured from a blood sample obtained from a storage bag. Additionally, claim 20, as recited, does not appear to exclude occurrence of in vitro erythrocyte hemolysis.

B) Applicant argues that levels of blood components present in stored blood will not behave similarly in the serum of patients with hemolysis and that hemoglobin levels in serum of patients do not necessarily correlate with hemolysis because of its removal from the bloodstream by various mechanisms. Accordingly, Applicant contends that hemoglobin is not an effective marker for low levels of hemolysis.

In response, Applicant's argument is not on point because the obviousness rejection based on the teaching of Olsson as set out by Examiner, is not limited to the relationship between hemolysis and hemoglobin alone. Instead, the obviousness rejection based on the teaching of Olsson is on the premise that adenylate kinase is released along with hemoglobin, at the time of red blood cell hemolysis. Accordingly,

test levels between adenylate kinase activity and hemoglobin concentration at the time of red blood cell hemolysis should have a direct correlation.

Allowable Subject Matter

11. Claims 24, 26, and 33-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Prior art of record does not teach or fairly suggest determining erythrocyte adenylate kinase activity by multiplying percentage erythrocyte adenylate kinase by the total amount of adenylate kinase activity, and using an antibody specific for erythrocyte adenylate kinase to bind erythrocyte adenylate kinase, to determine the presence of at least about 20 U/L erythrocyte adenylate kinase activity, and to thus diagnose erythrocyte hemolysis in a subject.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
January 6, 2005

Christopher L. Chin

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1/10/05